REMARKS

The Office Action has been carefully reviewed. Claims 3 and 44-46 are allowed. Claims 2, 4, 20-24, 38-40, 42 and 43 also presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Briefly, the present invention relates to a protein comprising the amino acid sequence of SEQ ID NO:3, a variant of SEQ ID NO:3 which has at least 90% identity therewith and most preferably at least 95% identity, or a fragment of SEQ ID NO:3, or a variant thereof, all of which are capable of binding to TRAF2. The present invention further relates to compositions comprising such proteins and antibodies capable of binding thereto.

Claims 2, 4, 20-24, and 38-43 have been rejected under 35 U.S.C. §112, first paragraph, because the examiner states that the specification, while being enabling for an isolated protein capable of binding to TRAF2 and having the amino acid sequence of SEQ ID NO:3, molecules which bind to this sequence and compositions comprising the protein, does not reasonably provide enablement for variants having 85%, 90% or 95% identity to SEQ ID NO:3 and having the ability to bind to TRAF2 or fragments of SEQ ID NO:3 that have the ability to bind to TRAF2. This rejection is respectfully traversed.

The enablement requirement of 35 U.S.C. §112 is discussed at section 2164 *et seq* of the MPEP. MPEP §2164.01 states that any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The question is whether the experimentation needed to practice the invention is undue or unreasonable. If the invention can be practiced without undue or unreasonable experimentation, the enablement requirement is considered to be met. The undue experimentation factors of *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) are set forth at MPEP §2164.01(a). These factors include:

(a) the breadth of the claims;

(b) the nature of the invention;

(c) the state of the prior art;

(d) the level of one of ordinary skill;

(e) the level of predictability in the art;

(f) the amount of direction provided by the inventor;

(g) the existence of working examples; and

(h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Here, the examiner takes the position that the scope of the claims is broader than the enabled disclosure with respect to variants of the disclosed protein sequence and fragments thereof.

The nature of the present invention is such that substantial experimentation is reasonably conducted by those of ordinary skill in the art. The present claims are directed to a protein of a specified amino acid sequence and fragments and variants thereof, including fragments of such variant which retain the ability to bind to TRAF2. Applicants concede that there is not 100% predictability in this field. However, this does not mean that an applicant must be limited to exemplified embodiments. As long as it is shown that the experimentation to determine what falls within the claim is not undue, the enablement requirement is met. As discussed in the arguments presented below, the experimentation is not undue.

Base claim 2 is now amended to recite for a variant having at least 90% sequence identity to the protein of SEQ ID NO:3.

In the rejection, the examiner has used an example of a protein having as high as 95% homology to SEQ ID NO:3, where the C-terminal 48 residues are completely different from those of SEQ ID NO:3 and where this 48 residue amino acid sequence can represent a functional domain for a protein which the examiner holds can also fold and function independently of the rest of the

protein. It is the examiner's position that the nature of the invention also includes protein domains that have not been discovered or made, which may have the ability to bind to TRAF2 either as a protein fragment or in the context of a larger protein.

With due respect to the examiner, the possibility that there may be a functional domain that folds and functions independently of the rest of the protein, similar to the situation in a fusion protein, is irrelevant. What is required by the claims is a polypeptide or fragment thereof that binds to TRAF2. As the recited protein, fragment, variant and fragment of the variant are all required to bind to TRAF2, it is clear that based on the high level of sequence identity (at least 90%), the variant would have a very similar primary structure to the protein of SEQ ID NO:3. If the examiner's example is examined further, by logic the remainder of the variant protein N-terminal to the C-terminal 48 residue would then have 100% identity to SEQ ID NO:3 if the variant had 95% identity to begin with. This would mean that the variant has a domain that clearly binds to TRAF2 regardless of whether or not there is an independently functioning domain which has no homology to SEQ ID NO:3 and can, for some unknown reason also fortuitously bind to TRAF2. Such a situation is analogous to a fusion protein in which the protein of SEQ ID NO:3 is fused to some other domain which folds and

functions independently of SEQ ID NO:3. Instant claim 3, which is allowed, is directed to a protein which comprises the amino acid sequence of SEQ ID NO:3. The scope of this claim is broad enough to encompass fusion of SEQ ID NO:3 to an independent functional protein or domain regardless of whether or not this protein or domain fused to SEQ ID NO:3 can bind to TRAF2.

Furthermore, it would also be well recognized by those of ordinary skill in the art that if the variant has high sequence identity to the protein of SEQ ID NO:3, then the fragment of the variant which binds to TRAF2 would be taken from a domain with high sequence identity to SEQ ID NO:3 rather from a domain of low sequence identity.

The above arguments also address the *Wands* factor relating to scope raised by the examiner. In addition, while claim 2 is somewhat broader than the specific sequence of (A), the claimed scope is necessary in order to reasonably cover the invention. In MPEP §2164.08, relating to enablement commensurate in scope with the claims, the MPEP quotes the following from *In re Goffe*, 191 USPQ 429, 431 (CCPA 1976):

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

It should be noted that the definitions of variants, and fragments of variants at claim 2(B) and (C), respectively, all require that the variants and fragments have the ability to bind to TRAF2. The proteins have utility merely by binding, for example in affinity chromatography, and, therefore, it is not absolutely necessary to assay for intracellular activity, although this can be done as taught on page 38 of the specification. In view of the stated activity and the direction in the specification, and the reasonable breadth of the variants, the breadth is not unduly broad and the experimentation to find everything within the scope of these claims would not be undue.

With regard to the state of the art, the examiner agrees that the art is silent concerning SEQ ID NO:3.

As to the level of one of ordinary skill in the art, inventions involving biotechnology involve a very high level of ordinary skill. Because of this extremely high level of ordinary skill, even complex experimentation is not necessarily undue or unreasonable. Furthermore, contrary to the examiner's assertion, function need not be assigned to a protein based on homology alone. Rather, with mere routine experimentation, one of ordinary skill in the art, which skill is very high, can readily determine variants within the scope of the sequence identity recited in the present claims that would have the ability to bind to TRAF2.

The next two *Wands* factors, the level of the predictability in the art and the amount of direction provided by the inventor, go hand in hand. As to the predictability in the art, when changing the sequence by 10% or less, more preferably 5% or less, there would be an expectation that the function is maintained. Thus, it is reasonably predictable that such a reasonably small number of random changes will work, but in any event, it is readily testable in order to determine which will have the claimed function and which will not have the claimed function. The present claim always requires that the result of the amino acid changes have the ability to bind to TRAF2, i.e., by definition, the activity must be retained. The present specification states on page 44, lines 11-20

> While any technique can be used to find potentially biologically active proteins which substantially correspond to TRAF2/NF-kB complex interacting proteins, one such technique is the use of conventional mutagenesis techniques on the DNA encoding the protein, resulting in a few modifications. The proteins expressed by such clones can then be screened for their ability to bind to TRAF2/NF-kB complex and to modulate TRAF/NF-kB complex activity in modulation/mediation activity of the intracellular pathways noted above.

The examiner takes the position that there are assays to identify what variants, fragments, and fragments of variants of SEQ ID NO:3 will bind to TRAF2 but they do not assist in the

ability to make and use these variants, fragments, and fragments of variants.

It is true that substantial experimentation will be necessary. However, as stated at MPEP §2164.06, the test is not merely quantitative since a considerable amount of experimentation is permissible if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Time and expense are not the controlling factors. Procedures for making variants of the protein of SEQ ID NO:3 which have at least 90% identity with the sequence thereof are conventional in the art, such as the technique detailed on pages 50-55 of the present specification. It is also well known to simply use random mutagenesis to generate a library for routine screening. Thus, the requirement for how to make is satisfied.

The assays involved to determine whether any such variant has the ability to bind TRAF2 are routine, as is disclosed in the specification and discussed above. All of the claimed variants must possess the specified activity of being able to bind TRAF2. There is a reduction to practice of the disclosed species of the protein of SEQ ID NO:3. The fact that any single amino acid change might have a profound effect or no effect, is not really dispositive. Here, standard binding assays

are known and so any given variant can readily be tested without undue experimentation. Indeed, whole libraries of variants can be tested simultaneously. Thus, applicants need not rely upon predictability of variants with respect to changes (even though there is reasonable predictability with variants of 90% or higher identity), but are relying on testing in the standard assays described in the specification and discussed above, which can be carried out in large numbers at the same time.

The level of skill in the art is high and the assays are standard and can be conducted with many different variant sequences at the same time. Thus, while substantial experimentation may be needed to establish all of the sequences of which fall within the scope of the claim, i.e., meet the functional requirement of binding to TRAF2, such experimentation is not undue or unreasonable. Indeed, for any given sequence, the testing is virtually negligible in order to test for binding to TRAF2.

The same is true with respect to fragments. Fragments can be made by removing one amino acid at a time from either end and testing for binding activity using the standard assays described in the specification and discussed above. Once the activity is lost, it would not be expected that smaller fragments would be operable. Thus, the amount of experimentation needed to find fragments is even less than that needed to find analogs.

With regard to how to use as discussed above, the variants and fragments thereof have utility merely by binding, for example in affinity chromatography.

For all these reasons, the enablement requirement is fulfilled. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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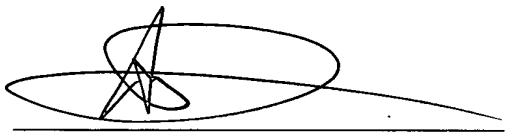
By 
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